CADTH

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**Caplacizumab (Cablivi) for Acquired thrombotic thrombocytopenic purpura (aTTP)**
Name of the Patient Group	**Answering TTP with the support of the Canadian Organization for Rare Disorders (CORD)**
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

Answering TTP – www. answeringttp.org

Answering TTP Foundation is located in Toronto, Ontario and solely made up of volunteers. There are five Directors of the Board with a diverse applicable skillsets. Two of the five Directors are also patients.

The operations team is made up of two members of the Board with help from a handful of volunteers. The Executive Director chairs the annual fundraiser and oversees the accounting with the help from a paid bookkeeper. The Chair runs the annual research competition, maintains the website, manages communications and educational materials and runs the day-to-day. Since its inception the Foundation has committed over $1.8 million to research grants through the end of 2020.

2. Information Gathering

Recruitment: All interview and survey questions were developed by CORD in collaboration with Answering TTP. The identification of interviewees and dissemination of the survey were done by Answering TTP, with outreach to all Answering TTP members through the website, Facebook, and direct email outreach. The interviews and summary of feedback were conducted by CORD with Answering TTP.

Responses: Patients provided input through a survey available on Survey Monkey from 26 July to 12 August 2019. The outreach was global and there was no restriction placed on the geographic location of the respondents. There were 289 respondents, four interviews and 257 completed online responses.

Diagnosis: Nearly half of the 257 survey respondents (45%) were between 20 and 39 years old when diagnosed with TTP; another 38% were diagnosed between 40 and 59 years of age. In terms of time since diagnosis, participants were split among four cohorts; 28% have been diagnosed for more than 10 years, 23% between 2 and 5 years, 21% between 5 and 10 years, and the remaining under two years,

Demographic information: Overall, 83% identified as the person with TTP; 7% were a parent or guardian, and 8% said they were a family member other than parent; remainder were professional

caregivers or patient advocates. In total, 88% of the persons diagnosed with TTP identified as female; 11% as male, and 1% preferred not to say.

About one-sixth (17%) of on-line respondents live in Canada while the majority, almost two-thirds (63%), report they are in the United States with a remaining 5% in Australia, 5% in the UK, and one-tenth (11%) elsewhere. Among the 40 Canadian survey respondents, 42% reside in Ontario with 16% in BC and 13% in Manitoba. There were equal percentages from Alberta and New Brunswick (8% each) with additional 5% from Nova Scotia and one each (3%) from Quebec, New Brunswick, and Saskatchewan. We analyzed separately responses from the Canadian cohort and those from rest of world. There were no differences in either qualitative or quantitative responses so this submission reflects the entire sample.

Both interviewed patients reside in Ontario, one having used caplacizumab and one not. The family members represent patients who had passed away. One family lived in Alberta and the other in the USA. The interviews were all conducted by the same interviewee by phone, using a semi-structured interview format. Interviews were not recorded but notes were taken with "verbatim" comments noted.

3. Disease Experience

“How the disease affects the patients; quality of life" were collected through several open-ended questions in the semi-structured interviews and one open-ended question in the survey. In addition, participants were asked to "rate" a number of symptoms commonly experienced during an episode of TTP with five fixed options anchored on one end by "no problem, never" and "minor, infrequent" to "serious, frequent" and "incapacitating, life-threatening" on the other end.

The most serious and frequently experienced symptoms during an episode of TTP were within the description, "Fever, fatigue, headache, migraines, dizzy spells, confusion", with more than 61% reporting these as "serious, frequent" or worse, with 17% rating these as "incapacitating, life threatening." Only 15% said they were "minor, infrequent" or "not at all." Similarly, more than half of survey respondents (53%) reported the experience of "bruises or red/purple spots on the skin" were "serious, frequent" or worse; only one-fifth (21%) reported these were "minor, infrequent" or less. Other common symptoms were "shortness of breath chest pain", reported as "serious, frequent” by one fourth (25%) but experienced by two-fifths (42%) as "minor, infrequent" or less impact.

Symptoms of "abdominal pain" and "kidney problems" were experienced similarly, with about one-fourth (25%) to one-fifth (20%) experiencing one or both as "serious, frequent" or worse, while about three-fifths (60%) said these were "not at all" or "minor, infrequent" occurrences. In contrast, about two-thirds (67%) to three-fourths (75%) said "strokes" and/or "bleeding (from gums, nose)" were "not at all" or "minor, infrequent" problems and less than one-fourth (24% to 15%) said these were "serious, frequent" or worse.

In terms of psychological or emotional effects, about one-third (34%) said these were "serious, frequent" or worse, while one-third (34%) said these effects were "no problem" or "minor, infrequent." Similarly, cognitive effects, presented as "Confusion and/or memory loss", were reported as "serious, frequent or worse" by one-third (34%) and "no problem" or "minor, infrequent" by another third (35%).

But these ratings cannot convey the real experience of living with aTTP. Unlike most chronic diseases, the challenge of aTTP is not the day-to-day experience, which may be characterized as remission when blood levels are normalized, but the acute TTP episode known as a "relapse", which can be life-threatening and requiring intensive treatment (plasma exchange). About half (49%) said they had experienced one or two relapses since diagnosis, while one-fifth (21%) had no relapses since remission. The remainder were about evenly distributed, from 13% who had had three-to-four relapses, 7% who had experienced five-to-six relapses and 7% who reported 7-to-10 or more relapses since their diagnosis.

To provide additional context, respondents were fairly evenly distributed in terms of time since last episode. A small percentage of respondents (14%) had experienced their last episode less than six months ago a and about the same percentage (12%) reported that they had been more than 10 years in remission. About one-fourth (26%) experienced their last episode between 6 months and 2 years ago, with almost one-third (30%) reporting they were two to five years post-episode and the remaining 18% had not had an episode for five to 10 years.

The verbatim comments presented here are drawn exclusively from the Canadian patients and families, therefore reflecting impact within the Canadian health, work, and social contexts.

IMPACT OF ACUTE EPISODE OF aTTP:

"… had never heard of this disease prior. …thanks to an emergency room Dr, that had attended a conference on autoimmune diseases. He connected the dots... I had mini strokes, platelet count of 7,000 and my body was shutting down. I was in ICU for three days, do not remember too much except for waking up to excruciating headaches. I received plasma transfusions and high doses of steroids. My family was traumatized to have me so sick.

"My mother died suddenly from TTP last year. We were devastated. The physicians did not recognize the disorder. She waited 3 hours in the emergency room only to die a few hours later."

"Even when responding to crisis you can lose them unless you act faster. Two big things contributing to death. Doctors took their time. Plasmapheresis happened quickly, but nobody was acting as if platelet drops and significant drops were serious. Second, they were overconfident based on initial response to PP; he was responding so well; platelets worked for a while. It was false confidence; 'Don't know why you are so worried; he won't die from this.' Sent him home. 9 or 10 days post diagnosis he passed."

AFTER aTTP EPISODE

"I had always been strong and hardly ever sick. This disease … completely changed my life. I was no longer able to have my home daycare and work with young children… and had to change careers. The financial burden was left up to my husband."

"… the side effects of the drugs take there [sic] toll. I had mood swings which made it sometimes hard interacting with my friends and family. The fear of relapse is always in the back of my mind."

"Impact on person affected, tired, hair loss, muscle pain, joint pain, memory issue, balance issue, muscle weakness, headaches, mood swings. Family, stress, always wondering when it will happen again. Financially, stressed as drugs are not covered because TTP not on list, so financially struggling."

RECURRING aTTP EPISODES

"… there was an emotional as well as financial toll. ...the illness which was literally diagnosed on my death bed. … financially it was problematic as the illness came back an additional seven times... I lost many months of wages due to being in hospital and being treated and recovering."

"TTP was a devastating diagnosis in my early 30s, followed my multiple relapses (6). It affected my ability to work; it had a profound effect on my ability to begin a family; resulted in panic attacks and depression; hospitalizations, surgery (splenectomy); adverse reactions to treatments."

"My life was ok until last week when I suffered a stroke while coming through my 4th episode. Now family life is completely disrupted."

LIFE DURING REMISSION

"My dreams of carrying a child were stolen by TTP... We have two girls born from surrogacy and egg donation. Many people can relate to issues of infertility, but less with the guilt of … knowing full well that perhaps one day you might succumb to TTP and leave your children motherless."

"I find that I am always 'foggy' with memory issues which made working difficult. Now ten years after first diagnosis I am no longer able to work."

"Difficult to impossible to get employment, also challenging to keep employment due to anger management issues due to various organ damage (stroke survival leaves you more emotional, kidney damage raises blood pressure.) ED issues have put strain on relationships."

"You are always on edge as you never know when it will reoccur. It is always in the back of your mind when travelling and doing day to activity, wear out a lot easier and always have that worry."

"Living in fear, my husband is tired, weak, has memory deficit. Kidney damage. Was diagnosed June 6th/19. Hospital until July16/19 and readmitted July 27/19. He is so frustrated, discouraged and our family is frightened about how this may end. Financially the impact of being out of town, costs involved is challenging."

4. Experiences With Currently Available Treatments

Specific treatments: benefits, side effects and management: Patients are generally diagnosed with aTTP during their first episode. There are two categories of treatment: Plasma exchange (aka plasmapheresis) and immune suppression therapies. Both are administered to deal with the urgent drop in platelets during an episode. Additional use of immune suppression therapies during remission may be used to reduce the likelihood of recurrence. However, there are no targeted or indicated treatments for TTP.

Among those who reported access to treatment, almost all (99%) reported receiving plasmapheresis (plasma exchange). Almost all (96%) had received corticosteroids (85% in the past and 11% currently). In terms of other drugs, about 70% had or were currently receiving rituximab and about 13% had or were receiving cyclosporine. Perhaps the only difference in treatment was "spleen removal" reported by 13% of the international cohort and 22% of Canadian respondents. Only 5-6% had received caplacizumab.

Effectiveness: Survey respondents were asked to rate effectiveness of each therapeutic intervention in managing TTP in terms of symptoms and progression, on a five-point scale anchored by "not at all" to "very well". For the majority of respondents (85%), plasmapheresis was regarded as effective, working "very well" (66%) or "well" (18%). The negative comments often referred to the fact that plasma exchange was not administered soon enough, there was not an immediate back-up strategy (guidelines or protocol) when the initial plasmapheresis did not sufficiently increase platelet count, or there was not the monitoring to assure that the platelet counts had stabilized (before discharge or post discharge).

"The ER did not appreciate the urgency of the severe platelet drop and did not start the plasma exchange right away."

"He was on plasmapheresis but the doctors were overconfident in the initial response to PP. He was responding so well; the platelets had risen so well, but it was false confidence. They recommended rituximab but it never got there. He passed away 9 or 10 days after diagnosis."

Challenges: Concerns were also raised about the inherent risks and challenges of plasma exchange. Many patients experience common adverse reactions, such as chills, fevers, urticaria, and itching, while others have experienced more serious events, including bleeding, infections, and anaphylactic shock. As a result, some patients may experience high anxiety and stress associated with the uncertainty of a possible adverse event while undergoing plasma exchange.

For most patients, the combination of therapies during and post-episode is critical.

“I had 18 days of plasmapheresis, and very high doses of prednisone. I am thankful that I was able to get rituximab, though I wish it was started earlier.”

“I feel it was the regimen the doctors provided that worked together, steroids, PLEX, vinchristine, cychlophosmide, and Rituxan that worked together.”

As noted in previous comments, however, the treatment with plasma exchange and other drugs was onerous, including the length of time on treatment, side effects, and lack of longer-term effectiveness.

"I did not respond very well to the treatment of aTTP in 2012. I stayed in the hospital for 3 months…."

"Bad side effects to some of those, but they did heal me."

"I could not stay on the steroids because of side effects."

"I had treatment with Rituximab for two separate instances, but it would only stave off the illness for at most a little over a year (13 or so months). After these initial fails, my doctors decided on spleen removal."

Moreover, spleen removal, often considered the treatment of last resort was often not perceived as effective (in preventing relapse) and certainly not without complications. Unfortunately, if all therapies have failed and the spleen has been removed, there are few options to prevent the next relapse.

"I did have major complications after spleen removal. Pneumonia, seizures, myocardial infarction x2."

"Cyclosporine hadn't worked. I tried Rituximab, 1 infusion every 3 months but then they found melanoma on my back. I had surgery and radiation for the melanoma …but there were now mets in my lung. With a history of TTP relapse, they took out the spleen before the immunotherapy. I am now Cancer free but I need a more targeted TTP fighting tool."

5. Improved Outcomes

Patients recognize plasmapheresis as the ubiquitous imperative treatment to deal with a TTP episode; however, it is not possible to over-emphasize the challenge of the process on the individual, both physically and emotionally, and by extension, the family. As described by one patient:

"Plasmapheresis treatments are tough. It feels as if your whole body is humming. … When I get a bag/a donor that I am more sensitive to, I might develop hives and get hot. As soon as I feel this, I would tell my nurse so she could give me another shot of Benadryl to counteract the reaction from the blood product. With every shot, I felt the rush of the Benadryl and I would try to give in and sleep. But mostly only my eyes close – the rest of my body is anxiously awake. I try not to think about the probability of a more serious reaction or side effect.

… Plasma exchange treatments save my life, but they also mean that my life is all of a sudden hijacked for extended hospital stays. This was easier when it just meant that I was off work and in hospital leaving my husband, parents, siblings and friends anxious about my recovery. This reaches a whole new level when you need to juggle kids and manage their emotions and real fears."

All respondents were presented with a brief summary of the drug and how it is used alongside plasmapheresis following an aTTP episode with the benefits of faster recovery and less risk of relapse.

In terms of expectations for outcomes, most respondents were "realistic" in focusing on the primary outcome as "normalizing platelet counts faster" with the short-term secondary outcomes then as shorter hospital stays, quicker return to normal life, and potentially higher survival. Some respondents also talked about the potential to decrease the likelihood of another episode (but this is more difficult to measure since relapses are not predictable and do not follow a predictable pattern, even within an individual.

Overall, while patients want interventions that work faster, better, and with greater likelihood of resolving the crisis, the most important outcome patients really want is the reduced possibility of a relapse, that is, no more episodes.

6. Experience With Drug Under Review

There were 12 respondents who had experience with caplacizumab, three who resided in Canada and nine elsewhere. Respondents had received the drug through clinical trials, special access, compassionate access, or extended trials. All of those who had received Caplacizumab spoke very positively. For those who have had episodes previously, it was remarkable that they were able to identify real differences in their response between recovery from other episodes without caplacizumab and their recovery with the addition of the drug. They spoke about time to response (platelet count recovery), time in hospital, and feeling of physical and mental well-being, specifically in terms energy and outlook.

"I believe that caplacizumab saved my life. My hematologist and nurses at the hospital were amazed by how quickly I responded to treatment, and as part of the extension trial, ….Knowing that a relapse may respond to treatment as well as my first bout with TTP due to caplacizumab has given me huge peace of mind and allowed me to be less fearful about the future."

"The most important benefit was … a quicker recovery when treated with plasmapheresis and steroids."

"Quick increase in platelets. Unsure of how it has affected my risk of relapse.

"The platelet count normalized very quickly, much quicker than plasma exchange alone and I was able to go home and get the rest of my treatment outpatient. Cablivi was easy to use and I had no side effects."

"A year ago, when I had my last relapse, I was not responding sufficiently to plasmapheresis and my doctor managed to get caplacizumab through special access. It was started in hospital (along with two doses of rituximab) but I finished treatment at home. My platelet count was rising slowly and then with the last dosage, it just skyrocketed, so I think it was taking my body a while to adapt to the wonder drug."

"Twice before I had rituximab but it made me feel sluggish. With this drug, I felt a lot 'lighter', not 'weighed down', and not so much a sense of 'doom and gloom' as with the rituximab."

Patients mentioned none-to-few side effects with caplacizumab; most of these were considered as minor and resolved after treatment was finished.

"Taking Cablivi did increase my anxiety because I started worrying about the side effects, I was having but it also made me feel better to see my platelets increase."

"My doctor said I may get a nosebleed or gum bleed, but that seemed very minimal for the miracle drug that it is."

"No side effects."

"The only minor side effect I experienced with caplacizumab was vaginal bleeding while I was taking the drug. This was not at all a deterrent to taking the drug, and I would absolutely take it again."

"Bleeding symptoms I have seen were all mild.".

"Bleeding gums were evident during treatment but have since resolved.

"Nose bleeds and bruising. Since I finished my treatment with the Cablivi I haven't had any issues with nose bleeds or bruising. It never was bad enough that I had to be taken off Cablivi."

Overall, all those who had experience with caplacizumab felt the drug definitely assisted in their time-to-recovery as well as keeping platelet counts at target level. They would want to have it available if they experienced another relapse and would definitely recommend the drug plans make it accessible to all.

"I think Cablivi would be great for most patients as long as they don't have a life-threatening risk of bleeding. For a first time diagnoses I think it would greatly help the patient return to normal life and would suffer less setbacks, memory loss or depression."

"Knowing that I will be guaranteed to have this again should I relapse is comforting."

Anything Else?

Patients want options to improve the likelihood of success of plasma exchange and to reduce the risk of future relapse. The family of one patient who had passed away stressed the value of any treatment that may reduce the likelihood of relapse. "Our daughter wanted to live her life to the fullest. She took the approach to travel with her fiancé to Bali and Japan, having researched ahead of time where she could be treated. Having a drug that would decrease the likelihood of a relapse would broadens your options."

"One of our frustrations was that she was getting plasmapheresis but the platelets [count] just didn't move. Having one more option could have made all the difference in the world."

"As soon as a TTP patient presents [with an episode], it is time to start treatment; there is no time for triage. Having a drug that is a "booster" could be very important. But even after the platelets seem to have stabilized, you have to continue to monitor. In our case, it dropped again over the weekend and by the time we realized he was in serious trouble, it was too late. He never got the rituximab or another drug. Our brother was robbed."

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Answering TTP Foundation

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   This submission was completed by Answering TTP with assistance of CORD No additional "outside help" was provided.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   Collection and analysis of this data was done by CORD and Answering TTP.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Sanofi silver sponsorship of annual fundraising event	$3,500			

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Sydney Kodastky
Position: Chair
Patient Group: Answering TTP Foundation
Date: September 30, 2019

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1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No, the survey and analysis were conducted by the Canadian Organization for Rare Disorders

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No, we have no one else entering the role.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Sanofi			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Durhane Wong-Rieger
Position: President & CEO
Patient Group: Canadian Organization for Rare Disorders
Date: 30 September 2019